

NEWS

Saving the Mind Faces High Hurdles

Fierce competition to find a drug that could delay onset of or prevent Alzheimer's disease is a relatively recent phenomenon. Why was this potential blockbuster shunned for so long?

Cancer has been arguably the most feared disease in the United States for the past several decades. Now, as the baby boom generation starts to inch past middle age, a new contender has emerged for that unappealing label: Alzheimer's disease (AD).

An estimated 4.5 million Americans already have the neurodegenerative condition, and that number could more than triple by 2050. Devastating to both those afflicted and their caregivers, the illness exerts a \$100-billion-a-year drain on the U.S. economy, according to the Biotechnology Industry Organization. "Alzheimer's disease probably has a larger impact on society than any other disease, in terms of economic and emotional costs," says Dale Schenk, chief scientific officer at Elan, a biotechnology company based in Dublin, Ireland.

So when *Science* looked for a condition that illustrates the challenges confronting the pharmaceutical industry—and the opportunities that beckon—AD was an obvious candidate. A drug that slows the disease could be especially lucrative because it presumably would need to be taken well before the first symptoms are likely to appear, and then for life. "Everyone recognizes that this is a great, unmet medical need. The drug company that succeeds here will be a very successful company," says Peter Boxer, associate director of central nervous system (CNS) pharmacology at Pfizer Global Research and Development in Ann Arbor, Michigan.

That recognition is fairly new, however. Academic and federal scientists had to lobby hard in the late 1980s to get Parke-Davis to conduct the first major clinical trial of an Alzheimer's drug. Although that drug, tacrine, and related compounds known as acetylcholinesterase inhibitors rang up about \$3 billion in sales for AD therapy in 2003, they are less than ideal medicines. They don't halt the underlying progression of the disease, and their slowing of cognitive decline is temporary.

But even a less-than-perfect AD drug could still be a blockbuster for companies.



Close look. By studying brain tissue from people who had Alzheimer's disease, drug companies are racing to develop drugs that slow or treat the disorder.

It would also be a boon for society: Because the prevalence of Alzheimer's disease increases exponentially with age, drugs that provide a modest 5-year delay in the onset

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of symptoms would reduce the number of affected people by as much as 50%.

Industrial nihilism

Although drug development for AD is a relatively young endeavor, the condition was identified nearly a century ago by German neuropathologist and psychiatrist Alois Alzheimer. In 1906, he gave a lecture on a 51-year-old woman who had died with dementia. An autopsy found that her brain was littered with extracellular masses (plaques) and intracellular clumps (neurofibrillary tangles) that have since become the diagnostic hallmark of the disease that now

bears his name. But for decades, because it wasn't diagnosable until after death, AD remained an obscure condition, and study of

the illness was a scientific backwater. "No one wanted to get into [AD research] because it was seen as an unpromising career path leading to a scientific dead end," recalls Zaven Khachaturian, former director of the Office of Alzheimer's Disease Research at the National Institute on Aging (NIA).

The same pessimism about AD held true in industry. "There was very little interest because the disease could not be diagnosed, and the prevailing wisdom considered it an untreatable normal consequence of aging," says Khachaturian. The lack of a cause was equally stifling to drug development. "There was a nihilism around [AD]," says neuroscientist Geoff Dunbar, who has worked on CNS drugs at several major companies and is now at a small biotech firm, Targacept, in Winston-Salem, North Carolina. "No one knew what to do with the plaques and tangles."

In the absence of hard evidence, a few vague theories took root. Some researchers argued that the dementia in general stemmed from inadequate blood flow within the brain, giving a slight boost to a class of drugs called cerebral vasodilators. Similarly, compounds that promoted learning and memory in animals—drugs known as nootropics, which means "growing the mind"—were also suggested as dementia treatments. "The assumption was that that would be sufficient to help the deficits in Alzheimer's disease," recalls Boxer.

The scientific hook

Drug development for AD didn't truly get started until the cholinergic hypothesis emerged in the late 1970s, largely through the efforts of British neuroscientists such as Peter Davies, now at Albert Einstein College of Medicine in New York City. In 1976, for example, he and a colleague reported that compared to normal brains, those from several people who had had the brain disorder had decreased levels of an enzyme that helps make the neuro-

CREDIT: SHON FRAISER/NEWCASTLE GENERAL HOSPITAL/PHOTO RESEARCHERS INC.

transmitter acetylcholine. Those data, combined with earlier evidence that drugs blocking the cholinergic system produced memory problems in people, led Davies and others to argue that the core defect in AD was a lack of acetylcholine.

"Until that time, dementia was primarily looked at as an amorphous mental disorder," says Khachaturian. "The cholinergic hypothesis was the first scientific hook that could provide a clear path to understand the underlying neurochemistry of AD. It also gave us a plausible scientific rationale for developing treatments because so much was known about the cholinergic system." That knowledge, says Dunbar, "meant we were in neuropharmacology that the industry understood."

There was also an obvious therapeutic road map to follow. It drew from work a decade earlier showing that the symptoms of Parkinson's disease stemmed from the death of dopamine-producing neurons and that L-dopa, a dopamine precursor, could bring about miraculous recoveries in patients. Could curing AD, researchers asked, be as simple as replacing acetylcholine?

Not quite. Efforts to deliver acetylcholine precursors to the brain met with little success. In 1986, however, a different strategy grabbed the spotlight. A research team reported remarkable benefits for a few AD patients taking the well-studied compound oral tetrahydroaminoacridine, also called tacrine, which blocks the activity of an enzyme that breaks down acetylcholine.

Quickly deciding to push for a validation study on the efficacy of tacrine, Khachaturian and the directors of the recently created, NIA-funded network of Alzheimer's Disease Research Centers sought a company to formulate the compound, which was off-patent, into various doses and quantities needed for a full-scale trial. They found an advocate in Elkan Gamzu at Parke-Davis. "Having a person inside that company lobbying for an efficacy study was very important to getting that first drug to go," says Khachaturian.

Parke-Davis, a division of Warner-Lambert Co. that later became part of Pfizer, started its tacrine study in 1987. But the drug, marketed as Cognex, failed to pass muster with a Food and Drug Administration (FDA) advisory board in 1991. After further trials with higher doses, the drug won FDA approval in 1993, albeit not without controversy. "The scientific community was not very enthusiastic about it because the benefits were marginal and it had a lot of side effects," says Khachaturian.

Still, its approval validated the cognitive tests that had recently been developed to gauge drug efficacy for the disease and provided clear guidelines on how to conduct clinical trials for AD. "If the FDA had set the



Double trouble. The pathological hallmarks of Alzheimer's disease are extracellular brain deposits of β amyloid called plaques (large blue oval in corner) and intracellular clumps of tau known as tangles (smaller blue masses).

bar very high and not approved it, then that would have been the kiss of death. No other company would have gotten into developing [AD] therapies," says Khachaturian. "Once tacrine was approved, a lot of other companies jumped on the bandwagon" to develop safer and more potent acetylcholinesterase

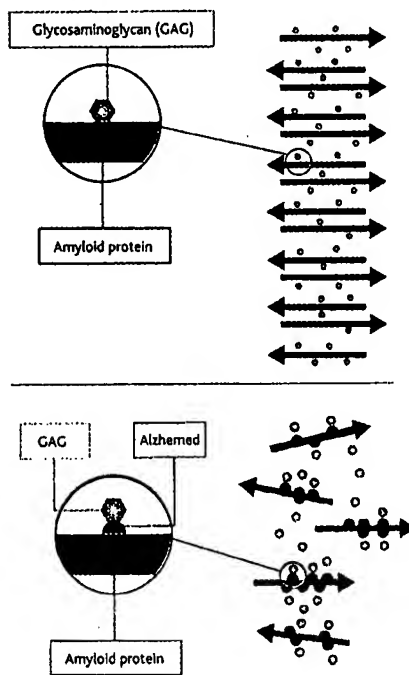
inhibitors, notes Boxer. (Six of the seven drugs currently approved in the U.S. for AD are in this class.)

The quick follow-up to tacrine by other drugs targeting the same enzyme illustrates an important principle of drug development. Even before a company with a head start on a target proves the value of a class of drugs, other firms will generally have similarly acting "me, too" drugs with improved properties in their pipeline. For competition's sake, says Boxer, "you can't wait for other companies' clinical data."

The acetylcholinesterase inhibitors spurred research into other ways of tweaking the cholinergic system. Acetylcholine operates through two classes of receptors, muscarinic and nicotinic, and major pharmaceutical companies vigorously pursued muscarinic agonists until troublesome side effects slowed their development. "Big pharma is still plugging away at the muscarinic hypothesis," says Dunbar. That has left room for his current firm, Targacept, to develop AD drugs that target nicotinic receptors.

The amyloid hypothesis

Still, halting the decline of the cholinergic system in AD is not the same as curing, preventing, or even slowing the actual pathology of the illness. In fact, the benefits of acetylcholinesterase inhibitors are so questionable that a government panel evaluating drugs for the U.K. health care system recently issued a preliminary opinion that the drugs aren't worth buying, a viewpoint the makers of the drugs have strongly challenged.



Keep apart? Now in phase III study, the drug Alzhemed blocks proteoglycan molecules from helping β amyloid form fibrils.

CREDITS (TOP TO BOTTOM): SHON FRAZER/PHOTO RESEARCHERS INC.; ADAPTED FROM THOMAS JEFFERSON UNIVERSITY

Most companies seeking more fundamental treatments for AD are focusing on a protein fragment called β amyloid, which in 1984 was shown to be the primary component of the brain's plaques. That discovery spawned the amyloid hypothesis, which holds that the buildup of β amyloid causes AD by harming or killing brain cells. In 1991, scientists found that several families plagued by an early-onset form of AD had mutations in the gene encoding β amyloid precursor protein (APP), from which β amyloid is derived. A few years later, similar disease-causing mutations were found in genes encoding proteins called presenilins that were subsequently shown to affect APP processing into β amyloid.

The amyloid hypothesis provided a bounty of new targets and potential strategies. Some companies tried to prevent β -amyloid molecules from clumping together, for example, while others began testing whether known drugs, such as statins and nonsteroidal anti-inflammatories, alter β -amyloid production.

The novel hypothesis opened the door for small biotech companies, too. Neurochem, which was founded in 1993 in Laval, Canada, drew upon research licensed from Queen's University in Kingston regarding proteoglycan molecules in the brain that bind to β amyloid and promote the formation of the amyloid fibrils that make up plaques. The company has developed small organic molecules that mimic these proteoglycans, occupying their binding sites on β amyloid and preventing fibrils. Earlier this year, Neurochem launched a phase III trial of its lead Alzheimer's treatment, Alzhemr, seeking to become the first to bring an amyloid-modifying drug to market.

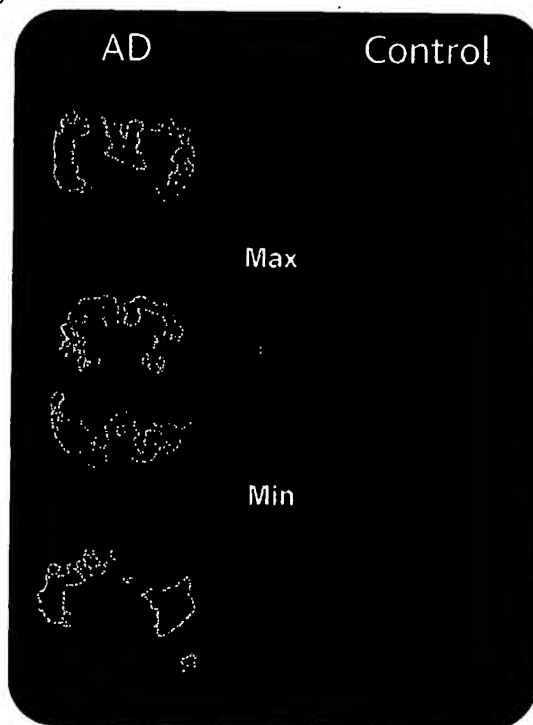
Few firms are trying to directly block β -amyloid molecules from aggregating, notes Dennis Garceau, senior vice president of drug development at Neurochem. "Big companies like to target enzymes; it's a more conventional target," he says. Indeed, the fiercest competition has been to develop secretase inhibitors, compounds that block the enzymes that cut APP into the smaller β -amyloid fragment.

The race began in 1999 when a β secretase that acts upon APP was identified. (After the initial published report by Amgen, several other firms quickly revealed that they too had identified the same potential β secretase, perhaps setting the stage for a patent fight.) "Everyone went after that target right away. It was such a rational target," says Boxer, who recalls hearing that another company had launched a major effort to inhibit the enzyme within a week of the announcement of its discovery.

The identified β secretase was a particularly inviting target because it belonged to the

same family of enzymes as HIV's protease. Several protease inhibitors had already been approved as AIDS drugs, allowing companies to draw on those experiences.

It takes two cuts to make β amyloid out of APP, however. Drug companies weren't ignoring the other key enzyme, γ secretase, but they just weren't clear what it was. A theory that presenilins were γ secretases took several years to



PET project. Using a compound developed at the University of Pittsburgh, researchers can now use PET scans to image the amount of β amyloid in brains of people with (left) or without (right) Alzheimer's disease. Such an ability could help drug companies monitor whether a drug is helping a person with Alzheimer's disease.

be accepted after its 1999 proposal. Still, even without a clear identification of the enzyme, several firms had developed in vitro systems displaying γ -secretase activity upon which they could test potential inhibitors.

Current efforts to develop secretase inhibitors remain shrouded in corporate secrecy. Bristol-Myers Squibb reportedly began clinical testing a γ -secretase inhibitor in 2001 and stopped because of side effects, but it has never publicly reported those results. Eli Lilly has also just begun clinical testing of a γ -secretase inhibitor. The challenge in developing such drugs seems to be blocking their action on enzymes needed for activities other than cutting up APP. γ secretases also cleave a protein called Notch, for example, that's important in development and the immune system. As a result, companies must find compounds that more specifically affect APP processing.

A surprise vaccine

While the amyloid hypothesis has offered drug researchers a number of obvious targets and strategies, it also led to the most surprising attempt to thwart AD. In the late 1990s, long after his colleagues at Elan had tested their most promising compounds, Schenk suggested injecting a few mice with β amyloid itself. His goal was to raise an antibody or other immune response against plaques. "No one thought it would work. Even after the experiment was done, the results weren't analyzed for a while," recalls Schenk.

The results were stunning. The immunization slowed or prevented the development of β -amyloid plaques in young mice and even wiped away preexisting ones in older mice. The episode illustrates how one person's idea can change the direction of a company or a field. "Dale was really brave," says John Trojanowski of the University of Pennsylvania School of Medicine in Philadelphia.

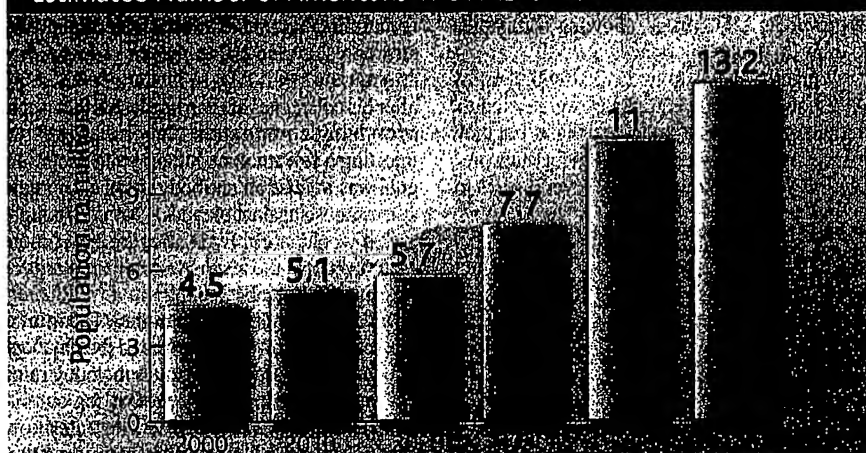
How does big pharma react when a disease-treating strategy such as the Elan vaccine comes out of the blue? Most large companies working on CNS drugs have experience with small-molecule drugs, not antibodies, says Boxer. And although firms can always tweak an enzyme inhibitor to make a better drug and carve out some market share, vaccines tend to either work or not. "We look at this stuff and go, 'Huh?'" says Boxer. "Where is your unique drug?" As result, he says, most companies have conceded the vaccine approach to Elan.

The unexpected emergence of the Elan vaccine illustrates the importance and limitations of animal models. For several years, companies pursuing the amyloid hypothesis were largely stuck in vitro. Attempts to genetically engineer mice that overproduced APP seemed fruitless; there was even a notable fraud case in which a researcher published a picture of a human plaque as evidence that his mice had developed β -amyloid clumps. "The entire field was trying to make a mouse model," says Schenk.

Then a failing biotech company trying to sell off its assets approached Elan and saved the day, ultimately setting the stage for the vaccine's proof of principle. The struggling company's transgenic rodents were greatly overexpressing APP, and when Elan scientists checked out the mice, they found numerous brain plaques. Elan acquired the rights to the mice and quickly began testing its compounds. The company eventually allowed the β -amyloid vaccine strategy to be tested. Without that animal model, the idea might have faded away.

Having animal models reduces the risk, and thus the cost, of developing drugs. For small

Estimated Number of Americans With Alzheimer's Disease



Going up. A number of factors influence predictions of how many Americans will have Alzheimer's disease in the coming years, but all such estimates suggest a rapid increase.

companies such as Neurochem, they can also be a lifeline to continued funding from venture capitalists and other sources. "Until we got proof of concept in vivo, people were a little bit skeptical," says Garceau.

Yet animal models also reveal the risks of drug development. Elan's vaccine approach seemed to work well in mice, but brain inflammation in a few patients triggered an abrupt halt to the clinical trial. Elan, together with its partner Wyeth, is now conducting clinical trials with plaque-targeting immunotherapy strategies such as passive administration of antibodies to β amyloid.

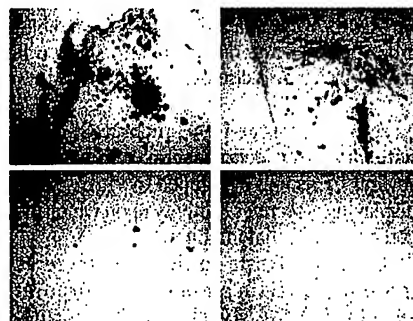
But how can a company pursuing β amyloid-based therapies for AD know if its drug or treatment is working? Showing that people maintain the same cognitive and memory skills, or improve such skills, can be difficult and time-consuming. Unfortunately, there are no well-accepted AD biomarkers, like cholesterol levels for heart disease or viral load for AIDS. A lack of animal models and biomarkers are "two difficult issues for developing a drug," says Boxer.

The biomarker obstacle has led companies such as Pfizer, Merck, Eli Lilly, and Elan to partner with the Alzheimer's Association, NIA, the National Institute of Biomedical Imaging and Bioengineering, and FDA to identify ways of measuring progression of mild cognitive impairment and AD in people. Industry will pick up one-third of the cost of the \$60 million, 5-year effort, known as the Alzheimer's Disease Neuroimaging Initiative, that will test various ways of imaging brain plaques and tangles as well as measuring levels of proteins in blood, urine, and cerebrospinal fluid. "It's so difficult [to develop an Alzheimer's treatment without biomarkers] that the drug companies are collaborating," says Boxer.

What about tau?

It's sometimes forgotten that the effort to develop β amyloid-based treatments represents a huge and costly gamble on a single, unverified theory of AD. There are many other hypotheses being explored by small numbers of scientists or a handful of tiny biotech firms. One is the second major theory of AD, which involves tangles, the intracellular brain lesions identified by Alois Alzheimer.

In the early days, Alzheimer's researchers were divided over whether plaques or tangles were more important. The identification of β amyloid in plaques and disease-causing mutations in the *APP* gene relegated tangles and their primary constituent, a hyperphosphorylated form of a protein called tau, to a



Surprise shot. Mice genetically engineered to overproduce β amyloid develop brain deposits (a, b) similar to the plaques in Alzheimer's disease, but injecting such rodents with β amyloid stirs an immune response that can clear such deposits (c, d).

sideshow. "We were the token other pathway at every meeting," recalls Trojanowski; he and his wife Virginia Lee have been the most vocal proponents of tangles and tau research.

For companies, that lack of interest was partly a matter of simple economics. "Even big pharma can only pick a certain number of targets," says Dunbar, noting that Bristol-Myers Squibb, where he used to direct clinical development of CNS drugs, has never had a tau program to his knowledge.

Tau is now drawing more attention, in part because of a 1998 paper in which researchers showed that mutations in a gene encoding one of the human versions of tau lead to a rare form of dementia that bears some similarities, such as tau tangles, to AD. "It launched studies that should have been done in the early 1990s," says Trojanowski.

Trojanowski contends that tau, when it becomes overloaded with phosphate groups, can no longer bind to and stabilize cellular filaments called microtubules. That change disrupts the ability of neurons to transport molecules down the long extensions known as axons. Back in 1994, his team proposed that microtubule-stabilizing compounds, such as the cancer drug Taxol, might treat AD. And earlier this year, in the 4 January *Proceedings of the National Academy of Sciences*, they offered a proof of concept in mice genetically engineered to overproduce a human version of tau.

These rodents suffer from a neurodegenerative disorder that includes tanglelike masses of hyperphosphorylated tau and impaired axon function. As hypothesized, the administration of Taxol sped up the animals' axonal transport and ameliorated their motor problems. Trojanowski and his colleagues are now working with Angiotech Pharmaceuticals in Vancouver, British Columbia, and other firms are sniffing around. "I know pharma is interested," he says. "My phone rings more often."

Partnerships and future

Will the next significant drug for AD come from a small biotech company or big pharma? Given the economics of drug development, it's likely that the Davids and Goliaths will end up working together.

"It's very difficult for a small company to take a drug all the way to market," notes Targacept's Dunbar. His company's strategy, for example, is to push a drug only through phase II trials and then "outsource it to big pharma." And Neurochem says it would be open to partnerships with bigger companies given the right deal.

Big pharma is certainly happy to let smaller companies take the initial plunge before it swoops in and buys up a promising drug. "They have such big wallets they can wait until almost all the risk is taken out," says Dunbar.

Still, the search for Alzheimer's drugs should leave room for many companies, small and large, to prosper. "This disease will need a cocktail of treatments," predicts Neurochem's Garceau.

—JOHN TRAVIS